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Beta-blockers in cirrhosis: Thank you for your attention

To the Editor:

We graciously thank Drs. Ferrarese, Thalheimer, their colleagues, and the editorial board and worldwide readership of the *Journal of Hepatology* for their interest in our article [1]. We are humbled and honored by the international attention that our article has received, and are excited by the debate that it has ignited within the hepatology community. We have received numerous positive correspondences regarding our review [2]. In light of recent studies that have stirred controversy, and in anticipation of future studies that will continue to stir controversy, we believed a fresh objective look at the emerging evidence in the use of beta-blockers in cirrhosis was warranted.

At our institution, our chief executive officer frequently impresses his mantra to "put patients first" upon our entire hospital staff [3]. As physicians, we all believe that what comes first is our relentless and selfless service and dedication to our patients. Sometimes, this involves challenging existing treatments when they are later found to be harmful, such as when the same investigator who first studied the benefits of beta-blockers in patients with cirrhosis no longer found these benefits universally applicable [4].

We have frequently cared for patients with advanced cirrhosis who were seemingly harmed by beta-blockers once they had fallen outside a certain "therapeutic window" (that had only recently been hypothesized) [5]. Once their beta-blockers were discontinued, azotemia, hypotension, and acute kidney injury frequently and convincingly resolved. We were certain other clinicians around the world must have encountered similar experiences, yet the scientific evidence appeared to be lacking. How could we turn our back on 30 years of highly cited landmark studies that promoted the use of beta-blockers? Did we miss something that was actually harming our patients?

Our article was therefore inspired by a need to re-explore the data. We do not dispute that the benefits of beta-blockers have been well-documented in patients with cirrhosis; however, that was not the focus of our article. We acknowledged these existing benefits and set out to more closely examine the studies that had been ignored [6], forgotten [7], or downplayed [8,9]. What we found was evidence – the quality of which can be debated, but nonetheless evidence stemming from astute clinicians making clinical observations – that beta-blockers were perhaps not as universally indicated as even we ourselves had previously believed. Just as the acetylsalicylic acid of cardiology has its limitations, the "aspirin of hepatology" appears to have its own pitfalls and limitations.

Even now, as this debate re-emerges, a new study from Mandorfer and colleagues provides fresh evidence demonstrating the detrimental effect of beta-blocker treatment after the development of spontaneous bacterial peritonitis [10]. More studies and debate are certain to follow.

We are extremely pleased that our review has achieved its intended effect of renewing dialogue and reopening the scrutiny on beta-blockers. We hope that this dialogue, along with new research specifically focusing at studying the end-stages of

cirrhosis, will continue to be encouraged by the international hepatology community.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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Is the pathway of energy metabolism modified in advanced cirrhosis?

To the Editor:
The role of metabolic alterations and adaptations is becoming increasingly evident in the pathogenesis of cirrhosis and hepatocellular carcinoma (HCC) [1–4]. Using a rat model of cirrhosis, Nishikawa *et al.* [5] demonstrate that early stage cirrhotic hepatocytes switch to glycolysis to meet their energy requirements as a result of a decline in oxidative phosphorylation, but that this mechanism fails in late cirrhosis. Since HCC typically arises in the background of liver cirrhosis [6] and also encompasses a glycolytic phenotype [7], it would be important to determine how this is related to the altered metabolism of cirrhotic hepatocytes. Since early cirrhotic cells are more glycolytic than advanced or failing cirrhotic cells, it remains unclear as to whether the progression of HCC is facilitated by metabolically active early cirrhotic cells or represents an escape mechanism of late cirrhotic hepatocytes which are unable to sustain their energy demands.

Conflict of interest

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